II. THE WITHDRAWAL OF PREVIOUS REJECTIONS

Applicants acknowledge the withdrawal of previous rejections set forth at page 2 of the final Office Action.

III. THE REJECTIONS UNDER 35 U.S.C. § 102/§ 103

A. THE REJECTION OVER SHEPARD

The final Office Action maintains the rejection of Claims 28-31, 37-38 and 40 under 35 U.S.C. § 102 as being anticipated by, or, in the alternative, under 35 U.S.C. § 103 as being obvious over, Shepard et al., J. Clin. Immunol., 11(3):117-27 (1991) ("Shepard"). In particular, the final Office Action asserts:

> [I]n the absence of evidence to the contrary, antibodies 7C2, 7F3, and 4D5 in the instant application are the same antibodies in the cited references because applicant Brian M. Fendly, of Genentech, Inc., is also the co-author on both cited references, which also list Genentech, Inc. as the address of correspondence. Both the instant application and the cited references also teach that antibodies bind to ErbB2. Therefore, the antibodies are the same because: 1) same laboratory, 2) same author/applicant, 3) same laboratory designation for the antibodies, 4) same procedures for producing antibodies, and 5) same reactivity, i.e., bind to ErbB2 (HER2).

Final Office Action at page 4. Applicants respectfully traverse the rejection.

A claim is anticipated under 35 U.S.C. §102 only if each and every element as set forth in the claim is found in a single prior art reference. Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." Richardson v. Suzuki Motor Co., 9 USPQ2d 1913 (Fed. Cir. 1989).

A claimed invention is unpatentable under 35 U.S.C. §103 if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a) (Supp. 1998); see Graham v. John Deere Co., 148 USPQ 459, 465 (1966). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. 148 USPQ at 467; Miles Labs, Inc., Inc. v. Shandon Inc., 27 USPQ2d 1123, 1128 (Fed. Cir. 1993).

"To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." MPEP § 2141, citing In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991).

Shepard does not anticipate or render obvious the claimed invention. The claimed invention is a method for inducing cell death that comprises exposing a cell that overexpresses ErbB2 to an effective amount of an isolated antibody that binds to Domain 1 of ErbB2 (Claims 28-31 and 37-38). Claim 40 further characterizes that the isolated antibody results in about 5 to 50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells.

Shepard discloses that the anti-p185^{HER2} murine monoclonal antibody (muMAb) 4D5 is directed at the extracellular domain (ECD) of the HER2 receptor and that the antibody has an effect as a result of modulating receptor function. Page 117, left column, page 119, left column, and page 125, right column.

The present inventors have surprisingly discovered that certain anti-ErbB2 antibodies, i.e., those that bind specifically to Domain 1 of the ECD of ErbB2, can induce death of an over expressing cell via apoptosis. As disclosed at page 13, lines 14-29, the term "induces cell death" refers to the ability of the antibody to make a viable cell become non-viable. Page 13, line 30 to page 14, line 12, of the specification discloses that the phrase "induce apoptosis" refers to the ability of the antibody to induce programmed cell death as determined by binding of annexin V, fragmentation of DNA, cell shrinkage, dilation of endoplasmic reticulum, cell fragmentation, and/or formation of membrane vesicles (called apoptopic bodies).

Furthermore, the claims require that the antibody is "isolated". As disclosed at page 19, lines 5-16, of the specification, the term "isolated antibody" refers to an antibody that has been identified and separated and/or recovered from a component of its natural environment, thus removing contaminant components of its natural environment that would otherwise interfere with its diagnostic or therapeutic uses, e.g., enzymes, hormones and other proteinaceous on non-proteinaceous solutes. Id.

As discussed in the Amendment submitted on March 29, 1999, the murine monoclonal antibody 4D5 disclosed in Shepard does not bind to Domain 1 of the ECD of ErbB2. See the specification at page 12, lines 6-29. Shepard therefore does not disclose or suggest the use of an isolated antibody that binds to Domain 1 of the ECD of ErbB2 to induce cell death.

Newly added Claims 56 and 57 depend on Claim 28. Applicants submit that for the

reasons discussed above, Shepard does not disclose or suggest the invention recited in Claims 56 and 57.

Reconsideration and withdrawal of the rejection of Claims 28-31, 37-38 and 40 under 35 U.S.C. § 102, or, in the alternative, under 35 U.S.C. § 103, over Shepard are respectfully requested.

B. THE REJECTION OVER LEWIS

The final Office Action maintains the rejection of Claims 28, 29, 37, 38 and 40 under 35 U.S.C. § 102 as being anticipated by, or, in the alternative, under 35 U.S.C. § 103 as being obvious over, Lewis et al., Cancer Immunol. Immunother., 37:255-63 (1993) ("Lewis"). In particular, the final Office Action asserts that the claimed invention is anticipated by or obvious over Lewis for the same reasons as discussed with regard to Shepard. Applicants respectfully traverse the rejection.

Lewis does not anticipate or render obvious the claimed invention. As discussed above, the claimed invention is a method for inducing cell death that comprises exposing a cell that overexpresses ErbB2 to an effective amount of an isolated antibody that binds to Domain 1 of ErbB2 (Claims 28, 29, 37, 38 and 40).

Lewis discloses the screening of a variety of different tumor cell lines for the expression of $p185^{HER2}$ using monoclonal antibodies directed against the ECD of the receptor. Page 255, left column. The reference discloses that a mouse/human chimeric 4D5 (chmAb 4D5) and a "humanized" 4D5 (rhu)mAb 4D5 HER2 antibody were constructed in order to increase the spectrum of tumor types potentially susceptible to monoclonal antibody-mediated anti-$p185^{HER2}$ therapies, to decrease potential immunogenicity issues with use of murine monoclonal antibodies

for human therapy, and to provide the potential for antibody-mediated cytotoxic activity. Page 255, left column. Page 256, left column, discloses that the authors "have constructed chimeric and humanized monoclonal antibodies derived from murine mAb 4D5 ... in order to provide the engineered monoclonal antibody with the ability to direct cytotoxic activity against the overexpressing tumor cells via antibody-dependent cellular cytotoxicity." Page 260, right column, discloses that chimeric mumAb 4D5 was prepared and employed as a substrate to generate a family of humanized variants, all of which contained the human IgG1 Fc region. Page 260, right column, and page 261, right column, discloses that "[i]t was [the authors'] hope that chimerizing or humanizing mumAb 4D5 with a human IgG1 constant region would enable the engineered monoclonal antibody to mediate immune cell killing of tumor targets overexpressing $p185^{HER2}$, and that this activity would be dependent upon overexpression of the receptor."

As discussed in the Amendment submitted March 29,1999, the humanized 4D5 disclosed in Lewis does not bind to Domain 1 of the ECD of ErbB2. See the specification at page 12, lines 6-29, and Fig. 13. Furthermore, although Lewis discloses that antibodies mumAb 2C4, mumAb 7F3 and mumAb 7C2 show overlapping activities corresponding to their shared epitopes, the reference does not disclose the binding of an antibody to Domain 1 of the ECD of ErbB2. Lewis therefore does not disclose or suggest the use of an isolated antibody that binds Domain 1 of the ECD of ErbB2 to induce cell death. Applicants further submit that, for the reasons discussed above, Lewis does not disclose or suggest the invention recited in newly added Claims 56 and 57.

Reconsideration and withdrawal of the rejection of Claims 28, 29, 37, 38 and 40 under 35 U.S.C. § 102, or, in the alternative, under 35 U.S.C. § 103, over Lewis are respectfully requested

IV. THE REJECTIONS UNDER 35 U.S.C. § 103

A. THE REJECTION OF CLAIMS 32-36 AND 39

The final Office Action maintains the rejection of Claims 32-36 and 39 under 35 U.S.C. § 103 as being obvious over Shepard or Lewis in view of Fendly et al., Cancer Res., 50:1550-8 (1990) ("Fendly"), Deshane et al., J. Invest. Med., 43 (Supp. 2):328A (1995) ("Deshane"), and further in view of Senter et al., U.S. Patent No. 4,975,278. In particular, the final Office Action asserts that the claimed invention is obvious over the cited references for the reasons discussed in Sections II and III above with regard to Shepard and Lewis. Applicants respectfully traverse the rejection.

Claims 32-36 and 39 depend from Claim 28. Thus, for the reasons discussed above, the primary references cited do not disclose or suggest the invention recited in these claims. Applicants further submit that Fendly, Deshane and Senter alone, combined with each other, and/or combined with Shepard and/or Lewis, do not disclose or suggest the claimed invention.

Claims 32-36 and 39 are directed to the method of Claim 28, wherein (1) the cell is also exposed to a second anti-ErbB2 antibody that does not bind to Domain 1 of ErbB2 (Claim 32); (2) the cell is also exposed to a second antibody that binds to ErbB2 and inhibits growth of SKBR3 cells in culture by 50-100% (Claims 33-36); and (3) the cell is further exposed to radiation (Claim 39).

Fendly discloses monoclonal antibodies specific for $p185^{HER2}$. Abstract. The monoclonal antibodies bind to the ECD of $p185^{HER2}$ and do not cross react with the epidermal growth factor receptor. Id. Page 1551, left column, discloses that the monoclonal antibodies were prepared by immunizing BALB/c mice. Page 1555, right column, discloses that the $p185^{HER2}$ monoclonal antibodies recognize at least four epitopes on the ECD of $p185^{HER2}$ and that monoclonal

antibodies 5B8 and 6E9 bind to epitopes very close to the transmembrane domain. The actual Domain bound, or the reason for concluding the location of binding, are not provided.

Deshane discloses the preparation of gene constructs to encode single chain immunoglobulins (sFvs) with anti-erbB2 specificity. The reference discloses that the use of the immunoglobulins in an anti-erbB2 polyclonal antibody demonstrate that expression of sFv results in down-regulation of cell surface erbB2.

Senter discloses a method for the delivery of cytotoxic drugs to tumor cells, wherein a tumor-specific antibody-enzyme conjugate is administered. Abstract.

As discussed above and in the Amendment submitted on March 29, 1999, the cited references do not disclose or suggest the use of an isolated antibody that binds to Domain 1 of the ECD of ErbB2 to induce cell death. Applicants further submit that the cited references do not disclose or suggest exposing the cell to a second anti-ErbB2 antibody that does not bind to Domain 1 of ErbB2. In addition, for the reasons discussed above, the cited references do not disclose or suggest the invention recited in newly added Claim 58.

Reconsideration and withdrawal of the rejection of Claims 32-36 and 39 under 35 U.S.C. §103 over Shepard, Lewis, Fendly, Deshane and Senter are respectfully requested.

B. THE REJECTION OF CLAIMS 42-55

The final Office Action rejects Claims 42-55 under 35 U.S.C. § 103 as being obvious over Shepard or Lewis in view of Fendly, Deshane, and further in view of Senter. In particular, the final Office Action asserts that the claimed invention is obvious over the cited references for the same reasons as discussed with regard to the rejections of claims 28-40 over Shepard and Lewis. Applicants respectfully traverse the rejection.

Claims 46-55 depend from Claim 28 . Thus, for the reasons discussed above, the cited references do not disclose or suggest the invention recited in these claims. Like Claim 28, Claims 42-45 are directed to a method for inducing cell death that comprises exposing a cell that overexpresses ErbB2 to an effective amount of an antibody that binds to Domain 1 of ErbB2. Thus, for the reasons discussed above, the cited references do not disclose or suggest the invention recited in Claims 42-45.

Reconsideration and withdrawal of the rejection of Claims 42-55 under 35 U.S.C. §103 over Shepard, Lewis, Fendly, Deshane and Senter are respectfully requested.

V. CONCLUSION

Early consideration and prompt allowance of the pending claims is respectfully requested. If there is anything that can be done to place the application in even better condition for allowance, Applicants request that the Examiner contact Applicants' representative at the telephone number listed below.

Respectfully submitted,

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